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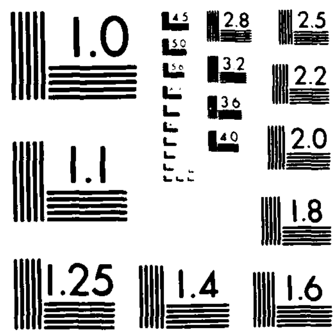

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19 ABSTRACT (Continue on reverse if necessary and identify by block number) The working hypothesis has been that long-term synaptic potentiation may mediate certain of the mnemonic functions of the hippocampal circuitry. The discovery of an underlying Hebbian conjunctive mechanism has boosted confidence in this hypothesis. One major effort of the past year was to summarize and integrate this AFOSR-supported discovery into a more general theoretical and experimental framework. The first step in this direction has been completed (galley proofs to follow). In regard to the 4 specific aims, development of the fluctuation algorithm has been completed, and it was applied to synaptic fluctuations obtained using the loose patch-clamp method (aim 2). The algorithm is currently running on a mainframe at UCLA. It is now being implemented on a small workstation (Macintosh II). As soon as it is working on the Mac II, the quantal analysis in hippocampus will begin (aim 1). The culture method is underway (aim 3) and a first-generation video microscopic technique was developed for visualizing neurons and their synapses to see if the latter move during activity (aim 4).

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A. Objectives

(1) General. The general goal is to understand how rapid and persistent forms of use-dependent forms of synaptic plasticity can combine with the neural circuit properties of certain forebrain structures to represent acquired information. The working hypothesis is that the phenomenon of long-term synaptic potentiation (LTP) is the most promising known synaptic change in the mammalian brain that could serve such a mnemonic function. The first step has been to learn more about the biophysical mechanisms underlying LTP. The motivation for this first step can be appreciated from the following sequence of questions, which were first raised in the AFOSR application. In terms of the molecular/biophysical mechanisms are there multiple forms of LTP? If there are multiple forms, are they controlled by different receptor mediated processes? Do the multiple forms result in different synaptic modification rules? Would these different rules result in qualitatively different adaptive changes in neural networks? Are higher forms of learning the result of concatenations of a variety of different synaptic modification mechanisms? Is this an essential design feature of neural architectures involved in intelligent or cognitive types of learning? The working assumption is that the answer to all of these questions is affirmative, but this has only been shown for the first two.

(2) Specific. To understand the molecular/biophysical mechanisms, some technical/analytical advances were necessary. The successful application of the single-electrode voltage clamp (SEC) to hippocampal synapses (Brown and Johnston, 1983) was the first step in this direction. The second step was to be able to apply the SEC to the study of LTP, which was more difficult because it required stable and long-term recordings using a low-resistance electrode. This has also now been accomplished (Barrionuevo et al, 1986; Griffith et al, 1986; Kelso et al, 1986). The present specific aims, listed below in the language of the contract, built upon these earlier advances.

(a) *Conduct quantal analysis experiments to determine the mechanism underlying LTP*. This analysis required looking at charge fluctuations under voltage-clamp conditions (hence the SEC). In addition, it required a new method of quantal analysis (Aim b below).

(b) *Develop patch-clamp technology and algorithms for fluctuation analysis*. This combination, when applied to the crayfish neuromuscular junction, is the most suitable way to create a new method of quantal analysis. Because the conditions for doing a quantal analysis in the acute hippocampal brain slice are far from perfect (see Aim c below), the goal here was to create the optimum method and to test it first under ideal conditions.

(c) *Develop and utilize the hippocampal slice culture preparation for studies of the role of individual neurons and synapses in LTP*. The cultured hippocampal slice preparation offers advantages not only for quantal studies but also for some of the other most powerful approaches to the cellular neurobiology of hippocampal synapses, including optical techniques (Aim d below).

(d) *Determine whether activity-dependent movement accompanies synaptic modifications during plasticity.* Synapses are now known to be much more plastic functionally than previously suspected. They may also undergo activity-dependent structural changes. Some popular hypotheses propose that the dendritic spines "twitch" during learning; others suggest that synapses actually relocate to new positions on the dendrites; still others propose that they divide or grow larger during learning. The idea is that with optically-improved tissue (such as the cultured slice preparation; aim c) combined with new microscopic methods (such as video microscopy and/or confocal scanning laser microscopy) one might actually be able to see living synapses and thus test some of these seemingly strange notions. Regardless of the correctness of these ideas, clearly it would be useful to be able to see synapses in the living state--if only to help perform the functional experiments.

B. Status

(1) General. The synthesis is being done in a series of articles, the first of which is completed (Brown et al, 1987). The galley proofs will arrive next week and will be forwarded at that time. A typed draft was previously sent to Dr. William Berry. This paper focusses on the molecular/ biophysical, subcellular, and single cell levels of analysis. It incorporates both published and previously unpublished experimental and theoretical work supported by the AFOSR. The theoretical work, based on compartmental neural simulations, turned out to be essential for understanding the role of dendrites and their spines in the induction and expression of LTP. In addition to developing the main ideas about LTP mechanisms, another purpose of the paper was to illustrate concretely the value of combining and integrating theoretical and experimental approaches. Although the AFOSR directorate does not need to be convinced of this, the majority of neuroscientists have remained aloof to or unaware of the power of a combined approach.

The second in this series, which was solicited by the editor of Nature magazine, will further amplify and illustrate the model for LTP induction developed in the first paper. It will compare and contrast that model with others that have been proposed by Timm Bliss, Ray Dingledine, and Christof Koch. It will suggest that there are two forms of hippocampal LTP--one of which is Hebbian and is controlled by the NMDA receptor. The model of Brown et al (1987) is suggested to be appropriate for the Hebbian form while Koch's may be appropriate for the non-Hebbian form. The two models can be formalized and simulated and they lead to differential and directly testable predictions. They have the virtue of being falsifiable.

Each of the subsequent manuscripts will focus at a slightly higher level. The final one in this series, which should be completed this year, will sketch out a network-level working hypothesis for the role of the hippocampal circuitry in the declarative memory system. The nice feature of this hypothesis is that it can be simulated and it leads to specific and testable predictions at the synaptic level.

(2) **Specific.**

(a) *Quantal analysis.* This will begin during the present year, as soon as the fluctuation method is implemented on the local workstation (Aim b below).

(b) *Fluctuation method*. This has been developed and is now running on a mainframe computer at UCLA. Loose patch-clamp data from the crayfish neuromuscular junction (Keenan and Brown, 1986) have been analyzed using this method and it seems to work. The approach uses a maximum-likelihood algorithm. It is provable that no other approach can do better in providing quantal parameters. Unlike the harmonic or deconvolution methods that this laboratory and others have explored, the maximum-likelihood approach furnishes standard errors of all of the parameter estimates. This is extremely important in evaluating (establishing "confidence levels" for) changes in quantal parameters during LTP.

In contrast to previous maximum-likelihood approaches to quantal analysis, this one utilizes more realistic models. First, the quantal size density distribution can be Gaussian or gamma distributed. Others have made the unrealistic assumption that there is no quantal variance. In the hippocampus there appears to be considerable quantal variance, based on voltage-clamp recordings of spontaneous miniature synaptic currents (Rong et al, 1987; Keenan and Brown, unpublished). Second, the probability release function can be Poisson, binomial, or a compound binomial. Others have assumed Poisson statistics, which this lab has shown are not appropriate (under most conditions) for hippocampus. Third, it assumes a Gaussian noise term, which can be directly assessed from the data. The typical model has 6 parameters, 2 of which are directly assessed from the data (mean and variance of the noise). Of the remaining 4, only 2 need to be relied upon for the present analysis (m, the mean quantal size and q, the mean quantal content).

Unfortunately, the computations take quite a while to run even on a mainframe. Attempting to get them to running them on an IBM AT therefore seemed unproductive. At the moment they are being installed on a Macintosh II workstation. Once the program is installed on the Mac II, it will be debugged and tested on the crayfish data (which have already been analyzed on the mainframe) as well as on simulated data. As soon as it passes both tests, it will be applied to hippocampal data. The latter should begin this year.

(c) *Cultured slices and microscopy*. The culture technique is just starting to work. The slices are surviving and beginning to flatten out to a monolayer. In addition, another culture method is about to be attempted. In principle, it offers much greater resolution. This technique, developed by Barbara Boss while in Maxwell Cowan's laboratory, enables "pure" cultures of monolayered granule cells sitting on a monolayer of glial cells. The upper surfaces of the granule cells are "bare", which is convenient both for patch-clamp recordings and for visualizing them. They appear to form mossy-fiber synapses with glia and themselves. This is probably the best possible preparation for visualizing synapses formed by a known hippocampal cell type. Barbara has raised antibodies that are specific for the mossy-fiber synapses. They bind to the vesicles, possibly to a zinc-binding protein.

(d) *Synaptic visualization*. The synaptic visualization project is proceeding nicely. Using video microscopy, it has been possible, even using acute brain slices, to visualize clearly the cell bodies of hippocampal neurons and their nuclei and nucleoli (Brown et al, 1987; Brown and Keenan, 1987). Under the best conditions, it is possible to see what seem to be the mossy-fiber synapses. With further developments of the microscopic techniques as well as the culture methods, the goal of seeing activity-dependent movement in hippocampal synapses appears to be achievable. More generally, the ability to visualize sub-cellular structures in the micron range opens up whole new vistas of inquiry.

C. Publications

(1) In print (1986)

Kelso, S.R., Ganong, A.H. and Brown, T.H. Postsynaptic control of LTP in hippocampus. Soc. Neurosci. Abstr. 12:506a, 1986.

Keenan, C.L. and Brown, T.H. Loose patch-clamp recordings of pre- and postsynaptic currents during long-term potentiation. Soc. Neurosci. Abstr. 12:506a, 1986.

Barrionuevo, G., Kelso, S., Johnston, D. and Brown, T. Conductance mechanism responsible for long-term potentiation in monosynaptic and isolated excitatory synaptic inputs to hippocampus. J. Neurophysiol. 55:540-550, 1986.

Griffith, W.H., Brown, T.H. and Johnston, D. Voltage-clamp analysis of synaptic inhibition during long-term potentiation in hippocampus. J. Neurophysiol. 55:767-775, 1986.

Kelso, S. and Brown, T.H. Differential conditioning of associative synaptic enhancement in hippocampal brain slices. Science 232:85-87, 1986.

Kelso, S., Ganong, A. and Brown, T.H. Hebbian synapses in hippocampus. Proc. Natl. Acad. Sci. 83:5326-5330, 1986.

(2) In press (1987)

Brown, T.H. and Keenan, C.L. Visualization of hippocampal synapses in brain slices using video microscopy. Soc. Neurosci. Abstr. 13:1987. In press.

Keenan, C.L., Baxter, D.A. and Brown, T.H. Multiplicative interaction between long-term potentiation and short-term facilitation in crayfish neuromuscular synapses. Soc. Neurosci. Abstr. 13:1987. In press.

Rong, X.-W., Keenan, C.L. and Brown, T.H. Single quantal currents in hippocampal neurons. Soc. Neurosci. Abstr. 13:1987. In press.

Ganong, A.H. and Brown, T.H. Role of NMDA-activated and voltage-dependent calcium channels in the induction of hippocampal long-term potentiation. Soc. Neurosci. Abstr. 13:1987. In press.

Rinaldi, P.C., Ganong, A.H. and Brown, T.H. Low-frequency synaptic depression recorded intracellularly from hippocampal granule cells. Soc. Neurosci. Abstr. 13:1987. In press.

Brown, T.H., Chang, V.C., Ganong, A.H., Keenan, C.L. and Kelso, S.R. Biophysical properties of dendrites and spines that may control the induction and expression of long-term synaptic potentiation. In: Long-term Potentiation: From Biophysics to Behavior, P.W. Landfield and S. Deadwyler (eds.), Alan R. Liss, 1987, pp. 197-260. In press.

(3) In preparation

Brown, T.H., Ganong, A., Kelso, S. and Keenan, C.L. Associative LTP. In: Neural Models of Plasticity, J.H. Byrne and W.O. Berry (eds.), Academic Press, 1987. In preparation.

Brown, T.H., Ganong, A., Keenan, C.L. and Kairiss, E. Hebbian synapses and glutamate receptors. Nature, 1987. In preparation.

Brown, T.H., Kairiss, E., Keenan, C.L., and Rinaldi, P. Context-dependent temporal linkages through autoassociative networks of the hippocampus. In: Adaptation, Learning and Affect, J. Madden, S. Matthysse and J. Barchas (eds.), Raven Press, 1988. In preparation.

D. Professional Personnel

(1) **Visiting Scientists** Patricia Rinaldi (Division of Neurosurgery, University of California at Irvine); Xin-Wei Rong (Shanghai Institute of Physiology)

(2) **Assistant Research Scientist** Claude L. Keenan

(3) **Postdoctoral Fellows** Alan H. Ganong; Edward W. Kairiss; German Barrionuevo (presently at Department of Psychobiology, University of Pittsburgh); Stephen Kelso (presently at Department of Biological Sciences, University of Illinois, Chicago)

(4) **Graduate students** Paul F. Chapman (Stanford University Ph.D. student in psychology; laboratory of Richard Thompson); Joanne Goh (University of British Columbia Ph.D. student in pharmacology; Laboratory of B.R. Sastry)

(5) **Undergraduate and high school students** Victoria Chang (Princeton University); Barbara Chang (San Marino High)

E. Interactions

(1) Presentations

(a) Seminars (Since 01/86)

05/15/87: "Biophysical and molecular mechanisms of long-term potentiation in hippocampus," Neuropsychiatric Institute, University of California, Los Angeles, CA

04/22/87: "Pseudo-Hebbian synapses and glutamate receptors," Beckman Research Institute of the City of Hope, Duarte, CA

04/10/87: "Pseudo-Hebbian synapses and the glutamate receptor," Brandeis University, Waltham, MA

04/08/87: "Long-term synaptic potentiation in the hippocampus," Yale University, New Haven, CT

03/13/87: "Pseudo-Hebbian synapses and the glutamate receptor," University of California, Irvine, CA

01/20/87: "Pseudo-Hebbian synapses and the glutamate receptor," Helmholtz Group Meeting, University of California, Irvine, CA

01/06/87: "Hebbian synapses in hippocampal circuits," Department of Neurobiology, NIH, Bethesda, MD

12/17/86: "Hebbian synapses in hippocampal circuits," California Institute of Technology, Pasadena, CA

12/01/86: "Hebbian synapses in Hippocampal Circuits," Yale University School of Medicine, New Haven, CT

10/07/86: "Cellular Analysis of Long-term Potentiation," University of Tennessee, Memphis, TN

02/19/86: "Neurophysiology of Long-term Potentiation," University of Southern California, Los Angeles, CA

01/23/86: "Synaptic Substrate for Learning," University of Southern California School of Medicine, Los Angeles, CA

(b) __Symposia and Workshops__ (Since 01/86)

1987: Workshop--"Central Synaptic Transmission" (Second World Congress of Neuroscience, Budapest, Hungary)

Symposium--"Neural Plasticity" (1987 Gordon Research Conferences, Wolfeboro, NH)

Symposium--"Competition and Cooperation in Neural Nets" (U.S.-Japan Seminar, University of Southern California, Los Angeles, CA)

Symposium--"Neural Models of Plasticity: Theoretical and Empirical Approaches" (Marine Biological Laboratory, Woods Hole, MA)

Workshop--"Long-term Potentiation: From Organism to Molecule" (11th Annual Conference on Learning and Memory, Park City, UT)

1986: Symposium--"Cellular Substrates of Learning: Vertebrate and Invertebrate" (16th Annual Society for Neuroscience Meeting Symposium, Washington, D.C.)

Symposium--"Experimental Analysis of Simple Neuronal Networks" (2nd Annual Symposium on Networks in Brain and Computer Architecture, North Texas State University, Denton, TX)

(2) **Consultative** N/A

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